Role of the microenvironment in human iPS and NSC fate and tumorigenesis

Grant Award Details

Role of the microenvironment in human iPS and NSC fate and tumorigenesis

Grant Type: Basic Biology II

Grant Number: RB2-01496

Project Objective: To investigate the role and influence of the microenvironment on the fate and tumorigenesis of NSCs derived from stem cells.

Investigator:

Name:	Aileen Anderson
Institution:	University of California, Irvine
Type:	PI

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Name:	Masaya Nakamura
Institution:	Keio University
Type:	Partner-PI

Disease Focus: Spinal Cord Injury, Neurological Disorders

Collaborative Funder: Japan

Human Stem Cell Use: Adult Stem Cell, Embryonic Stem Cell

Award Value: $1,256,194

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Role of the microenvironment in human iPS and NSC fate and tumorigenesis

Public Abstract: Multipotent Neural Stem Cells (NSC) can be derived from adult central nervous system (CNS) tissue, embryonic stem cells (ESC), or iPSC and provide a partially committed cell population that has not exhibited evidence of tumorigenesis after long term CNS transplantation. Transplantation of NSC from these different sources has been shown by multiple investigators in different CNS injury and disease paradigms to promote recovery or ameliorate disease. Additionally, both {REDACTED} groups have shown that human NSCs transplanted in the subacute period after spinal cord injury promote functional recovery. While the role of the host immune response has been considered in the context of immune-rejection, predominantly regarding the T-cell response, the consequence of an ongoing inflammatory response within the context of the tissue microenvironment for cell fate, migration, and integration/efficacy has been largely overlooked. Critically, the tumorigeneis, fate, migration, and integration/repair potential of a stem cell is driven by: 1) the intrinsic properties of cell programming, e.g., the type and source of cell / means used to derive the cell, and maintenance/differentiation of the cell in vitro; and 2) the extrinsic factors the cell encounters. Variations in the intrinsic properties of the cell may affect the potential of that cell for uncontrolled proliferation or the response of the cell to extrinsic factors that it later encounters, defining its fate, migration, and integration/repair potential. The {REDACTED} group has demonstrated that iPS-derived neurospheres (iPS-NS) exhibit a surprisingly large degree of variation in tumorigenesis potential after CNS transplantation, which is correlated with tissue source as well as differentiation and NS forming capacity. Moreover, the intrinsic properties of hNSC populations derived from different cell sources have not been broadly characterized; in fact, {REDACTED} has published the first data in the field demonstrating the differences in fate and integration/repair potential between primary and secondary neurospheres generated via in vitro differentiation of mouse or human ESC and iPSC. In parallel, {REDACTED} has shown profound differences in the response of NSC derived from human tissue versus hESC to extrinsic signals. Together, these data suggest that both characterization of the intrinsic properties of NSCs derived from different sources is essential for our understanding of the basic biology of these cells. Investigation of molecules and signaling pathways directing hNSC fate choices in the injured CNS microenvironment will yield new insight into the mechanisms of fate and migration decisions in these cell populations.

Statement of Benefit to California:	Multipotent Neural Stem Cells (NSC) can be derived from adult central nervous system (CNS) tissue, embryonic stem cells (ESC), or induced pluripotent cells (iPSC) and provide a partially committed cell population that has not exhibited evidence of tumorigenesis after long term CNS transplantation. Transplantation of NSC from these different sources has been shown by multiple investigators in different CNS injury and disease paradigms to promote recovery or ameliorate disease. Accordingly, stem cell based therapeutics such as these have the potential to treat a variety of traumatic, congenital, and acquired human conditions. However, while much progress has been made, translational research with human stem cell populations will remain limited by the progress of the fundamental understanding of the basic biology of these cells. The {REDACTED} group has pioneered understanding the critical role of timing in considering cell transplantation therapies. More recently, this group has focused on the neural induction of mouse- and human-derived iPSC and tested the potential of these cell populations for spinal cord injury treatment in animal models. {REDACTED} has established the NOD-scid mouse as a model for experimental neurotransplantation for xenograft studies, characterizing the relationship between transplant timing, engraftment outcome, cell fate, host remyelination, and functional recovery. Recently, this group has focused on how the innate inflammatory response influences cell fate and migration. In this collaborative proposal, researchers from California and Japan propose to combine their expertise to characterize and investigate some of the most fundamental aspects of the intrinsic properties of, and extrinsic factors influencing, human induced pluripotent (hiPSC) and human embryonic (hESC) stem cells, pooling knowledge and expertise in stem cell and animal model paradigms. The experiments proposed investigate the basic cellular and molecular mechanisms underlying the role of the host environment in stem cell fate regulation, and the relationship between reprogramming and tumorigenic/fate potential of hiPS-NSC in vitro and after transplantation, and key to this collaborative effort, the interface of these two aspects of basic stem cell biology. Critically, this international collaboration combines the expertise of two of the most advanced laboratories in translational stem cell biology to address several key unresolved questions in the control of cell fate, and will promote sharing of resources, data, and techniques between these labs to advance the field. Ultimately, the collaborative work proposed may permit the development of strategies to refine cellular reprogramming techniques, alter in vitro differentiation strategies, or manipulate the microenvironment to maximize the window for potential stem cell-based neurotherapeutics.